ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
0.26 - 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix.

After reconstitution with the solvent provided, the concentration of cetrorelix is 0.25 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 0.25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide 0.25 mg should only be prescribed by a specialist experienced in this field.

Cetrotide 0.25 mg is for subcutaneous injection into the lower abdominal wall.

Cetrotide 0.25 mg can be administered by the patient herself after appropriate instructions by her doctor.

For instructions for use and handling, see section 6.6.

The contents of 1 vial (0.25 mg cetrorelix) are to be administered once daily, at 24 h intervals, either in the morning or in the evening.

Administration in the morning: Treatment with Cetrotide 0.25 mg should commence on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with Cetrotide 0.25 mg should commence on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

4.3 Contra-indications

- Hypersensitivity to cetrorelix acetate, extrinsic peptide hormones or mannitol.
- Pregnancy and lactation.

- Postmenopausal women.

- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and special precautions for use

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 0.25 mg during a repeated ovarian stimulation procedure. Therefore Cetrotide 0.25 mg should be used in repeated cycles only after a careful risk/benefit evaluation.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

4.6 Pregnancy and lactation

Cetrotide 0.25 mg is not intended to be used during pregnancy and lactation (see section 4.3 „Contra-indications“).

Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the drug was administered during the sensitive phase of gestation.

4.7 Effects on ability to drive and use machines

Due to its pharmacological profile cetrorelix is unlikely to impair the patient’s ability to drive or to operate machinery.

4.8 Undesirable effects

Mild and transient reactions at the injection site, e.g. erythema, itching, and swelling.

Occasionally systemic side effects, e.g. nausea and headache have been reported. In addition, a single case of pruritus has been reported during treatment with Cetrorelix.

A severe hypersensitivity reaction, associated with cough, rash and hypotension, was observed in one patient after 7 months of treatment of ovarian cancer with cetrorelix (10 mg/day). The patient recovered completely within 20 minutes. A causal relationship could not be excluded.

Occasionally an ovarian hyperstimulation syndrome can occur which is an intrinsic risk of the stimulation procedure (see section 4.4 „Special warnings and precautions for use“).

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: LHRH-Antagonist, ATC code: H01CC02.

Cetrorelix is a luteinising hormone releasing hormone (LHRH) antagonist. LHRH binds to membrane receptors on pituitary cells. Cetrorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetrorelix controls the secretion of gonadotropins (LH and FSH).

Cetrorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetrorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. Following a single dose of 3 mg of cetrorelix a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetrorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetrorelix were fully reversible after termination of treatment.

5.2 Pharmacokinetic properties

The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.

The total plasma clearance and the renal clearance are 1.2 ml x min^{-1} x kg^{-1} and 0.1 ml x min^{-1} x kg^{-1} , respectively. The volume of distribution ($V_{d,area}$) is 1.1 l x kg^{-1}. The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site. The subcutaneous administration of single doses (0.25 mg to 3 mg cetrorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetrorelix. No signs of drug-related local irritation or incompatibility were noted in dogs after intravenous, intra-arterial and paravenous injection when cetrorelix was administered in doses clearly above the intended clinical use in man.

Cetrorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, water for injections

6.2 Incompatibilities

As cetrorelix is incompatible with several substances of common parenteral solutions it should be dissolved only by using water for injections.

6.3 Shelflife

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the container in the outer carton.

6.5 Nature and content of container

Packs with 1 or 7 Type I glass vials each containing 55.7 mg powder for solution for injection sealed with a rubber stopper.

Additionally for each vial the packs contain:

1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 1 ml solvent for parenteral use
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

6.6 Instructions for use and handling, and disposal

Cetrotide 0.25 mg should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 0.23 mg cetrorelix.

The solution should be used immediately after reconstitution.

The injection site should be varied daily.

7. MARKETING AUTHORISATION HOLDER

ASTA Medica Aktiengesellschaft
An der Pikardie 10
01227 Dresden
Germany

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/..../...../..../....

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 3 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
3.12 - 3.24 mg cetrorelix acetate equivalent to 3 mg cetrorelix.

After reconstitution with the solvent provided, the concentration of cetrorelix is 1 mg/ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 3 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide 3 mg should only be prescribed by a specialist experienced in this field.

Cetrotide 3 mg is for subcutaneous injection into the lower abdominal wall.

Cetrotide 3 mg can be administered by the patient herself after appropriate instructions by her doctor.

For instructions for use and handling, see section 6.6.

The contents of 1 vial (3 mg cetrorelix) are to be administered on day 7 of ovarian stimulation (approximately 132 to 144 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins.

If the follicle growth does not allow ovulation induction on the fifth day after injection of Cetrotide 3 mg, additionally 0.25 mg cetrorelix (Cetrotide 0.25 mg) should be administered once daily beginning 96 hours after the injection of Cetrotide 3 mg until the day of ovulation induction.

4.3 Contra-indications

- Hypersensitivity to cetrorelix acetate, extrinsic peptide hormones or mannitol.
- Pregnancy, and lactation.
- Postmenopausal women.
- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and special precautions for use

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 3 mg during a repeated ovarian stimulation procedure. Therefore Cetrotide 3 mg should be used in repeated cycles only after a careful risk/benefit evaluation.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

4.6 Pregnancy and lactation

Cetrotide 3 mg is not intended to be used during pregnancy and lactation (see section 4.3 „Contra-indications“).

Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the drug was administered during the sensitive phase of gestation.

4.7 Effects on ability to drive and use machines

Due to its pharmacological profile cetrorelix is unlikely to impair the patient’s ability to drive or to operate machinery.

4.8 Undesirable effects

Mild and transient reactions at the injection site e.g. erythema, itching, and swelling.

Occasionally systemic side effects, e.g. nausea and headache have been reported. In addition, a single case of pruritus has been reported during treatment with Cetrorelix.

A severe hypersensitivity reaction, associated with cough, rash and hypotension, was observed in one patient after 7 months of treatment of ovarian cancer with cetrorelix (10 mg/day). The patient recovered completely within 20 minutes. A causal relationship could not be excluded.

Occasionally an ovarian hyperstimulation syndrome can occur which is an intrinsic risk of the stimulation procedure (see section 4.4 „Special warnings and precautions for use“).

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: LHRH-Antagonist, ATC code: H01CC02.

Cetrorelix is a luteinising hormone releasing hormone (LHRH) antagonist. LHRH binds to membrane receptors on pituitary cells. Cetrorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetrorelix controls the secretion of gonadotropins (LH and FSH).

Cetrorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetrorelix delays the LH surge and consequently ovulation.

In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. Following a single dose of 3 mg of cetrorelix a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetrorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetrorelix were fully reversible after termination of treatment.

5.2 Pharmacokinetic properties

The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.

The total plasma clearance and the renal clearance are 1.2 ml x min^{-1} x kg^{-1} and 0.1 ml x min^{-1} x kg^{-1} ,respectively. The volume of distribution ($V_{d,area}$) is 1.1 l x kg^{-1}. The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site. The subcutaneous administration of single doses (0.25 mg to 3 mg cetrorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetrorelix. No signs of drug-related local irritation or incompatibility were noted in dogs after intravenous, intra-arterial and paravenous injection when cetrorelix was administered in doses clearly above the intended clinical use in man.

Cetrorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, water for injections

6.2 Incompatibilities

As cetrorelix is incompatible with several substances of common parenteral solutions it should be dissolved only by using water for injections.

6.3 Shelflife

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the container in the outer carton.

6.5 Nature and content of container

Pack with 1 Type I glass vial containing 167.7 mg powder for solution for injection sealed with a rubber stopper.

Additionally the pack contains:

1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 3 ml solvent for parenteral use
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

6.6 Instructions for use and handling, and disposal

Cetrotide 3 mg should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 2,82 mg cetrorelix.

The solution should be used immediately after reconstitution.

7. MARKETING AUTHORISATION HOLDER

ASTA Medica Aktiengesellschaft
An der Pikardie 10
01277 Dresden
Germany

8. NUMBER IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/..../...../..../....

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

- ASTA Medica Aktiengesellschaft, Weismüllerstraße 45, D-60341 Frankfurt, Germany.

Manufacturing Authorisation issued on 7 November 1997 by the Bezirksregierung Detmold, Germany.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

Text for Outer Carton (Pack with 1 Vial)

Cetrotide 0.25 mg powder and solvent for solution for injection
Cetrorelix (as acetate)

1 vial with powder for solution for injection.
1 pre-filled syringe with solvent for parenteral use.

1 vial with 55.7 mg powder contains:
0.26 - 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix.
Excipient: Mannitol.

1 pre-filled syringe with solvent contains:
1 ml water for injections.

Subcutaneous use.
Reconstitute only with the solvent provided.
For single use only.

Keep out of the reach and sight of children.

Expiry date:
Use immediately after reconstitution.

Do not store above 25 °C. Keep the container in the outer carton.

ASTA Medica AG
An der Pikardie 10
01277 Dresden
Germany

EU/..../..../..../....

Lot:
Lot of the solvent:

Medicinal product subject to medical prescription.

Text for Outer Carton (Pack with 7 Vials)

Cetrotide 0.25 mg powder and solvent for solution for injection
Cetrorelix (as acetate)

7 vials with powder for solution for injection.
7 pre-filled syringes with solvent for parenteral use.

1 vial with 55.7 mg powder contains:
0.26 - 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix.
Excipient: Mannitol.

1 pre-filled syringe with solvent contains:
1 ml water for injections.

Subcutaneous use.
Reconstitute only with the solvent provided.
For single use only.

Keep out of the reach and sight of children.

Expiry date:
Use immediately after reconstitution.

Do not store above 25 °C. Keep the container in the outer carton.

ASTA Medica AG
An der Pikardie 10
01277 Dresden
Germany

EU/..../..../..../....

Lot:
Lot of the solvent:

Medicinal product subject to medical prescription.

Texts for Vial and Pre-filled Syringe

Vial

Cetrotide 0.25 mg
Cetrorelix (as acetate)

Subcutaneous use.

Exp.:

Lot:

55.7 mg

Pre-filled syringe

Solvent for Cetrotide 0.25 mg

1 ml water for injections

Exp.:

Lot.:

Text for Outer Carton

Cetrotide 3 mg powder and solvent for solution for injection
Cetrorelix (as acetate)

1 vial with powder for solution for injection.
1 pre-filled syringe with solvent for parenteral use.

1 vial with 167.7 mg powder contains:
3.12 - 3.24 mg cetrorelix acetate equivalent to 3 mg cetrorelix.
Excipient: Mannitol.

1 pre-filled syringe with solvent contains:
3 ml water for injections.

Subcutaneous use.
Reconstitute only with the solvent provided.
For single use only.

Keep out of the reach and sight of children.

Expiry date:
Use immediately after reconstitution.

Do not store above 25 °C. Keep the container in the outer carton.

ASTA Medica AG
An der Pikardie 10
01277 Dresden
Germany

EU/..../..../..../....

Lot:
Lot of the solvent:

Medicinal product subject to medical prescription.

Texts for Vial and Pre-filled Syringe

Vial

Cetrotide 3 mg
Cetrorelix (as acetate)

Subcutaneous use.

Exp.:

Lot:

167.7 mg

Pre-filled syringe

Solvent for Cetrotide 3 mg

3 ml water for injections

Exp.:

Lot.:

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Please read this leaflet carefully because it contains important information for you. If you have further questions, please ask your doctor or your pharmacist. This medicine has been prescribed for you personally, and you should not pass it on to others.

PRODUCT NAME

Cetrotide 0.25 mg powder and solvent for solution for injection
Cetrorelix (as acetate)

QUALITATIVE AND QUANTITATIVE COMPOSITION
What are the components of Cetrotide 0.25 mg?

One vial with 55.7 mg powder containing as active substance 0.26 - 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix. Additionally, the powder contains mannitol as excipient.

One pre-filled syringe containing 1 ml water for injections.

MARKETING AUTHORISATION HOLDER AND MANUFACTURER
Who is responsible for the marketing and manufacture of Cetrotide 0.25 mg?

Marketing Authorisation Holder

ASTA Medica Aktiengesellschaft
An der Pikardie 10
01277 Dresden
Germany

Manufacturer

ASTA Medica Aktiengesellschaft
Weismüllerstraße 45
60314 Frankfurt
Germany

PHARMACEUTICAL FORM AND CONTENTS
What does Cetrotide 0.25 mg consist of?

Cetrotide 0.25 mg is a powder for solution for injection. It is available in packs of one or seven vials.

Additionally, for each vial the packs contain

- one pre-filled syringe with solvent (water for injections) for parenteral use for dissolving the powder in the vial
- one injection needle with a yellow mark for injecting the water into the vial and withdrawing the solution from the vial
- one injection needle with a grey mark for injecting the solution
- two alcohol swabs for cleaning purposes.

PHARMACOTHERAPEUTIC GROUP
How does Cetrotide 0.25 mg work?

Cetrotide 0.25 mg inhibits the effects of a natural hormone, called luteinising hormone releasing hormone (LHRH). LHRH regulates the secretion of another hormone, called luteinising hormone (LH), which induces ovulation during the menstrual cycle. Cetrotide 0.25 mg inhibits premature ovulation which is undesirable during hormone treatment for ovarian stimulation as only mature egg cells are suitable for fertilisation.

THERAPEUTIC INDICATIONS
Why use Cetrotide 0.25 mg?

Cetrotide 0.25 mg is used to prevent premature ovulation during a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 0.25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle stimulating hormone (FSH) suggested similar efficacy. HMG and FSH are hormones promoting egg maturation.

CONTRA-INDICATIONS
When should you not use Cetrotide 0.25 mg?

Do not use Cetrotide 0.25 mg if you

- are allergic to cetrorelix acetate, mannitol or exogenous peptide hormones (medicines similar to Cetrotide 0.25 mg)
- are pregnant or breast-feeding
- have already reached your menopause
- have a moderate or severe kidney or liver disease.

PRECAUTIONS FOR USE
What precautions have to be taken?

During or following hormonal stimulation of the ovaries an ovarian hyperstimulation syndrome can occur. This event is related to the stimulation procedure with gonadotropins (hormones promoting egg maturation). For symptoms and suitable measures please refer to the Patient Information Leaflet of the gonadotropin-containing medicine prescribed for you.

Luteal phase support (a measure to support the onset of pregnancy) should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 0.25 mg during a repeated ovarian stimulation procedure. Therefore you should use Cetrotide 0.25 mg in repeated cycles only after a careful risk/benefit evaluation by your doctor.

SPECIAL WARNINGS
Driving and using machines?

As far as it is known, Cetrotide 0.25 mg does not impair your ability to drive or to operate machinery.

What special precautions should pregnant or breast-feeding women take?

You should not use Cetrotide 0.25 mg if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.

INTERACTIONS

What other products influence the effect of Cetrotide 0.25 mg and what other products can Cetrotide 0.25 mg effect?

Experimental investigations have shown that interactions are unlikely with medications that are metabolised in the liver. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

INSTRUCTIONS FOR PROPER USE

How much of Cetrotide 0.25 mg should you use and how often should you use it?

The following statements apply to Cetrotide 0.25 mg unless otherwise prescribed by your doctor. Please observe these instructions for use, otherwise you will not fully benefit from Cetrotide 0.25 mg.

The contents of one vial (0.25 mg Cetrorelix) are to be administered once daily, at 24 h intervals, either in the morning or in the evening.

Administration in the morning: Treatment with Cetrotide 0.25 mg should begin on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with Cetrotide 0.25 mg should begin on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

How should you use Cetrotide 0.25 mg?

You may self-administer Cetrotide 0.25 mg after appropriate instruction from your doctor.

Cetrotide 0.25 mg is for injection under the skin of the lower abdominal wall, preferably around the navel. To minimise local irritation, please select a different injection site each day.

Dissolve Cetrotide 0.25 mg powder only with the water contained in the pre-filled syringe. Do not use a Cetrotide 0.25 mg solution if it contains particles or if it is not clear.

Before you administer Cetrotide 0.25 mg yourself, please read the following instructions carefully:

1. Wash your hands. It is important that your hands and all items you use are as clean as possible.

2. Lay out on a clean surface everything you need (one vial, one pre-filled syringe, one injection needle with a yellow mark, one injection needle with a grey mark and two alcohol swabs).

3. Flip off the plastic cover of the vial. Wipe the aluminium ring and the rubber stopper with an alcohol swab.

4. Take the injection needle with the yellow mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Put the needle on the syringe and remove the cover of the needle.

5. Push the needle through the centre of the rubber stopper of the vial. Inject the water into the vial by slowly pushing the plunger of the syringe.

6. Leave the syringe on the vial. Gently agitate the vial until the solution is clear and without residue. Avoid forming bubbles during dissolution.

7. Draw the whole contents of the vial into the syringe. If solution is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.

8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Put the needle on the syringe and remove the cover of the needle.

9. Invert the syringe and push the plunger until all air bubbles have been expelled. Do not touch the needle or allow the needle to touch any surface.

10. Choose an injection site at the lower abdominal wall, preferably around the navel. Take the second alcohol swab and clean the skin at the injection site. Hold the syringe in one hand. Gently pinch up the skin surrounding the site of injection and hold firmly with the other hand.

11. Hold the syringe as you would hold a pencil, insert the needle completely into the skin at an angle of about 45 degree.

12. Once the needle has been inserted completely, release your grasp of the skin.

13. Pull back gently the plunger of the syringe. If blood appears continue as described in step 14. If no blood appears, inject the solution slowly by pushing the plunger gently forward. After all of the solution is injected, withdraw the needle slowly, applying gentle pressure with the alcohol swab on the skin where the needle was inserted. Withdraw the needle at the same angle as it was inserted.

14. If blood appears, withdraw the needle with the syringe and gently apply pressure to the injection site. Do not use this solution but empty the syringe in a sink. Start again with step 1.

15. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury).

SPECIAL ADVICE

What do you do if you have used too much of Cetrotide 0.25 mg?

Overdosage of Cetrotide 0.25 mg may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects. Therefore, in case of overdosage no specific measures are required.

What to do if you miss a dose?

If you missed to administer Cetrotide 0.25 mg on one day, please contact your doctor immediately and ask for advice.

Ideally Cetrotide 0.25 mg should be administered at 24 hours intervals. But if you missed to administer Cetrotide 0.25 mg at the right time it is no problem to administer this dose at a different time of the same day.

SIDE EFFECTS

What undesirable effects may Cetrotide 0.25 mg cause?

Mild and transient reactions may occur at the injection site like reddening, itching, and swelling.

Occasionally systemic side effects, like nausea and headache have been reported. In addition, a single case of pruritus has been reported during treatment with Cetrorelix..

A severe hypersensitivity reaction, associated with cough, rash and hypotension, was observed in one patient after 7 months of treatment of ovarian cancer with cetrorelix (10 mg/day). The patient recovered completely within 20 minutes. A causal relationship could not be excluded.

Occasionally, stimulation of ovaries with gonadotropins (hormones promoting egg maturation) may lead to a so-called ovarian hyperstimulation syndrome (OHSS). Symptoms like abdominal pain, tension, nausea, vomiting, diarrhoea and breathing difficulties may indicate an OHSS. Please inform your doctor immediately, if you feel such symptoms.

If you notice any unwanted effect not mentioned in this leaflet or if you are unsure about the effect of this medicine, please inform your doctor or pharmacist.

STORAGE INSTRUCTIONS

How long can you keep Cetrotide 0.25 mg?

The Cetrotide 0.25 mg powder in the vial and the solvent in the pre-filled syringe have the same expiry date. It is printed on the labels and on the carton. Do not use the Cetrotide 0.25 mg powder or the solvent after this date.

How long can you keep Cetrotide 0.25 mg after preparation of the solution?

The solution should be used immediately after preparation.

Store the medicine out of the reach of children.

How is Cetrotide 0.25 mg to be stored?

Do not store above 25°C. Keep the container in the outer carton in order to protect it from light.

DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED

When was this leaflet prepared?

If you have any further questions please consult your doctor or pharmacist.

Further information
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder**.**

België/Belgique/Belgien
ASTA Medica S.A./N.V.
Rue de l'Etuve 77 - 81
Stoofstraat 77 - 81
B-1000 Bruxelles/Brussel/Brüssel
Tel.: +32 2 5040811

Danmark
ASTA Medica AB
Kemistvägen 17
S-18379 Täby
Tel.: +46 8 7580040

Deutschland
ASTA Medica AWD GmbH
Weismüllerstaße 45
D-60314 Frankfurt
Tel.: +49 69 400101

Ελλάδα
ΦΑΡΜΑΛΕΞ Α.Ε.Β.Ε.
Τσόχα 15-17
GR-115 10 Αθήνα
Τηλ.: +30 1 64 45 612

España
ASTA Medica S.A.U.
Avda Fuentemar 27
E-28820 Coslada (Madrid)
Tel.: +34 91 6699300

France
Laboratoire ASTA Medica
Avenue J. F. Kennedy-B.P.. 100
F-33701 Merignac Cedex
Tel.: +33 5 56 55 35 35

Ireland
ASTA Medica Ltd
168 Cowley Road
Cambridge CB4 0DL, UK
Tel.: +44 1223 423434

Italia
Industria Farmaceutici
Serono S.p.A.
Via Casilina
I-00176 Roma
Tel.: +39 06 703841

Luxembourg/Luxemburg
ASTA Medica S.A.
Rue del´ Etuve 77 - 81
B-1000 Bruxelles/ Brüssel
Tel.: +32 2 5040811

Nederland
ASTA Medica B.V.
Postbus 171
NL-1110 BC Diemen
Tel.: +31 20 6903121

Österreich
ASTA Medica
Arzneimittel Ges.m.b.H.
Liesinger Flur-Gasse 2c
A-1230 Wien
Tel.: +43 1 86390-0

Portugal
ASTA Medica
Produtos Farmacêuticos, Lda
Rua do Centro Cultural, 13
P-1749-066 Lisboa
Tel.: +351 1 8420300

Suomi/Finland
ASTA Medica
Tiedotuskeskus
Kehräsaari
FIN-33200 Tampere
Tel.: +358 3 2228890

Sverige
ASTA Medica AB
Kemistvägen 17
S-18379 Täby
Tel.: +46 8 7580040

United Kingdom
ASTA Medica Ltd
168 Cowley Road
Cambridge CB4 0DL, UK
Tel.: +44 1223 423434

PACKAGE LEAFLET

Please read this leaflet carefully because it contains important information for you. If you have further questions, please ask your doctor or your pharmacist. This medicine has been prescribed for you personally, and you should not pass it on to others.

PRODUCT NAME

Cetrotide 3 mg powder and solvent for solution for injection
Cetrorelix (as acetate)

QUALITATIVE AND QUANTITATIVE COMPOSITION
What are the components of Cetrotide 3 mg?

One vial with 167.7 mg powder containing as active substance 3.12 - 3.24 mg cetrorelix acetate equivalent to 3 mg cetrorelix. Additionally, the powder contains mannitol as excipient.

One pre-filled syringe containing 3 ml water for injections.

MARKETING AUTHORISATION HOLDER AND MANUFACTURER
Who is responsible for the marketing and manufacture of Cetrotide 3 mg?

Marketing Authorisation Holder

ASTA Medica Aktiengesellschaft
An der Pikardie 10
01277 Dresden
Germany

Manufacturer

ASTA Medica Aktiengesellschaft
Weismüllerstraße 45
60314 Frankfurt
Germany

PHARMACEUTICAL FORM AND CONTENTS
What does Cetrotide 3 mg consist of?

Cetrotide 3 mg is a powder for solution for injection. It is available in a pack with one vial.

Additionally the pack contains

- one pre-filled syringe with solvent (water for injections) for parenteral use for dissolving the powder in the vial
- one injection needle with a yellow mark for injecting the water into the vial and withdrawing the solution from the vial
- one injection needle with a grey mark for injecting the solution
- two alcohol swabs for cleaning purposes.

PHARMACOTHERAPEUTIC GROUP
How does Cetrotide 3 mg work?

Cetrotide 3 mg inhibits the effects of a natural hormone, called luteinising hormone releasing hormone (LHRH). LHRH regulates the secretion of another hormone, called luteinising hormone (LH), which induces ovulation during the menstrual cycle. Cetrotide 3 mg inhibits premature ovulation which is undesirable during hormone treatment for ovarian stimulation as only mature egg cells are suitable for fertilisation.

THERAPEUTIC INDICATIONS

Why use Cetrotide 3 mg?

Cetrotide 3 mg is used to prevent premature ovulation during a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 3 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle stimulating hormone (FSH) suggested similar efficacy. HMG and FSH are hormones promoting egg maturation.

CONTRA-INDICATIONS

When should you not use Cetrotide 3 mg?

Do not use Cetrotide 3 mg if you

- are allergic to cetrorelix acetate, mannitol or exogenous peptide hormones (medicines similar to Cetrotide 3 mg)
- are pregnant or breast-feeding
- have already reached your menopause
- have a moderate or severe kidney or liver disease.

PRECAUTIONS FOR USE

What precautions have to be taken?

During or following hormonal stimulation of the ovaries an ovarian hyperstimulation syndrome can occur. This event is related to the stimulation procedure with gonadotropins (hormones promoting egg maturation). For symptoms and suitable measures please refer to the Patient Information Leaflet of the gonadotropin-containing medicine prescribed for you.

Luteal phase support (a measure to support the onset of pregnancy) should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 3 mg during a repeated ovarian stimulation procedure. Therefore you should use Cetrotide 3 mg in repeated cycles only after a careful risk/benefit evaluation by your doctor.

SPECIAL WARNINGS

Driving and using machines

As far as it is known, Cetrotide 3 mg does not impair your ability to drive or to operate machinery.

What special precautions should pregnant or breast-feeding women take?

You should not use Cetrotide 3 mg if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.

INTERACTIONS

What other products influence the effect of Cetrotide 3 mg and what other products can Cetrotide 3 mg effect?

Experimental investigations have shown that interactions are unlikely with medications that are metabolised in the liver. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

INSTRUCTIONS FOR PROPER USE

How much of Cetrotide 3 mg should you use and how often should you use it?

The following statements apply to Cetrotide 3 mg unless otherwise prescribed by your doctor. Please observe these instructions for use, otherwise you will not fully benefit from Cetrotide 3 mg.

The contents of 1 vial (3 mg cetrorelix) are to be administered on day 7 of ovarian stimulation (approximately 132 to 144 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins.

A single dose of Cetrotide 3 mg results in a duration of action of at least 4 days. If the follicle growth does not allow ovulation induction on the fifth day after injection of Cetrotide 3 mg, additionally 0.25 mg cetrorelix (Cetrotide 0.25 mg) should be administered once daily beginning 96 hours after the injection of Cetrotide 3 mg until the day of ovulation induction.

How should you use Cetrotide 3 mg?

You may self-administer Cetrotide 3 mg after appropriate instruction from your doctor.

Cetrotide 3 mg is for injection under the skin of the lower abdominal wall, preferably around the navel.

Dissolve Cetrotide 3 mg powder only with the water contained in the pre-filled syringe. Do not use a Cetrotide 3 mg solution if it contains particles or if it is not clear.

Before you administer Cetrotide 3 mg yourself, please read the following instructions carefully:

1. Wash your hands. It is important that your hands and all items you use are as clean as possible.

2. Lay out on a clean surface everything you need (one vial, one pre-filled syringe, one injection needle with a yellow mark, one injection needle with a grey mark and two alcohol swabs).

3. Flip off the plastic cover of the vial. Wipe the aluminium ring and the rubber stopper with an alcohol swab.

4. Take the injection needle with the yellow mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Put the needle on the syringe and remove the cover of the needle.

5. Push the needle through the centre of the rubber stopper of the vial. Inject the water into the vial by slowly pushing the plunger of the syringe.

6. Leave the syringe on the vial. Gently agitate the vial until the solution is clear and without residue. Avoid forming bubbles during dissolution.

7. Draw the whole contents of the vial into the syringe. If solution is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.

8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Put the needle on the syringe and remove the cover of the needle.

9. Invert the syringe and push the plunger until all air bubbles have been expelled. Do not touch the needle or allow the needle to touch any surface.

10. Choose an injection site at the lower abdominal wall, preferably around the navel. Take the second alcohol swab and clean the skin at the injection site. Hold the syringe in one hand. Gently pinch up the skin surrounding the site of injection and hold firmly with the other hand.

11. Hold the syringe as you would hold a pencil, insert the needle completely into the skin at an angle of about 45 degree.

12. Once the needle has been inserted completely, release your grasp of the skin.

13. Pull back gently the plunger of the syringe. If blood appears continue as described in step 14. If no blood appears, inject the solution slowly by pushing the plunger gently forward. After all of the solution is injected, withdraw the needle slowly, applying gentle pressure with the alcohol swab on the skin where the needle was inserted. Withdraw the needle at the same angle as it was inserted.

14. If blood appears, withdraw the needle with the syringe and gently apply pressure to the injection site. Do not use this solution but empty the syringe in a sink.

15. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury).

SPECIAL ADVICE

What do you do if you have used too much Cetrotide 3 mg?

Overdosage of Cetrotide 3 mg may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects. Therefore, in case of overdosage no specific measures are required.

What to do if you miss a dose?

If you missed to administer Cetrotide 3 mg, please contact your doctor immediately and ask for advice.

SIDE EFFECTS

What undesirable effects may Cetrotide 3 mg cause?

Mild and transient reactions may occur at the injection site like reddening, itching, and swelling.

Occasionally systemic side effects, like nausea and headache have been reported. In addition, a single case of pruritus has been reported during treatment with Cetrorelix.

A severe hypersensitivity reaction, associated with cough, rash and hypotension, was observed in one patient after 7 months of treatment of ovarian cancer with cetrorelix (10 mg/day). The patient recovered completely within 20 minutes. A causal relationship could not be excluded.

Occasionally, stimulation of ovaries with gonadotropins (hormones promoting egg maturation) may lead to a so-called ovarian hyperstimulation syndrome (OHSS). Symptoms like abdominal pain, tension, nausea, vomiting, diarrhoea and breathing difficulties may indicate an OHSS. Please inform your doctor immediately, if you feel such symptoms.
If you notice any unwanted effect not mentioned in this leaflet or if you are unsure about the effect of this medicine, please inform your doctor or pharmacist.

STORAGE INSTRUCTIONS

How long can you keep Cetrotide 3 mg?

The Cetrotide 3 mg powder in the vial and the solvent in the pre-filled syringe have the same expiry date. It is printed on the labels and on the carton. Do not use the Cetrotide 3 mg powder or the solvent after this date.

How long can you keep Cetrotide 3 mg after preparation of the solution?

The solution should be used immediately after preparation.

Store the medicine out of the reach of children.

How is Cetrotide 3 mg to be stored?

Do not store above 25°C. Keep the container in the outer carton in order to protect it from light.

DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED
When was this leaflet prepared?

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Ελλάδα
ΦΑΡΜΑΛΕΞ Α.Ε.Β.Ε.
Τσόχα 15-17
GR-115 10 Αθήνα
Τηλ.: +30 1 64 45 612

España
ASTA Medica S.A.U.
Avda Fuentemar 27
E-28820 Coslada (Madrid)
Tel.: +34 91 6699300

France
Laboratoire ASTA Medica
Avenue J. F. Kennedy-B.P.. 100
F-33701 Merignac Cedex
Tel.: +33 5 56 55 35 35

Ireland
ASTA Medica Ltd
168 Cowley Road
Cambridge CB4 0DL, UK
Tel.: +44 1223 423434

Italia
Industria Farmaceutici
Serono S.p.A.
Via Casilina
I-00176 Roma
Tel.: +39 06 703841

Luxembourg/Luxemburg
ASTA Medica S.A.
Rue del´ Etuve 77 - 81
B-1000 Bruxelles/ Brüssel
Tel.: +32 2 5040811

Nederland
ASTA Medica B.V.
Postbus 171
NL-1110 BC Diemen
Tel.: +31 20 6903121

Österreich
ASTA Medica
Arzneimittel Ges.m.b.H.
Liesinger Flur-Gasse 2c
A-1230 Wien
Tel.: +43 1 86390-0

Portugal
ASTA Medica
Produtos Farmacêuticos, Lda
Rua do Centro Cultural, 13
P-1749-066 Lisboa
Tel.: +351 1 8420300

Suomi/Finland
ASTA Medica
Tiedotuskeskus
Kehräsaari
FIN-33200 Tampere
Tel.: +358 3 2228890

Sverige
ASTA Medica AB
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S-18379 Täby
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United Kingdom
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168 Cowley Road
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